REMARKS

Claim 83 has been amended to specifically recite that the differential gene expression profile is determined by using a genomic-based bioassay method and replace the term "molecular markers" with "genes". Support for this amendment can be found at least in the title and the specification at page 21, lines 9 to 10; page 28, lines 5 to 14; page 44, lines 7 to 12; and page 44, lines 16 to 17. Claim 83 has also been amended to insert "(e)" to further define the steps of the claimed method. Addition of "(e)" only relates to formality of Claim 83 and does not alter the claimed subject matter in any way. Claim 84 has been amended to delete "*in vitro* assays". New Claim 88 has been added reciting that the genomic-based bioassay method is selected from the group consisting of gene microarrays, polymerase chain reaction (PCR), cDNA arrays, and oligonucleotide arrays. Support for the new claim can be found at least in the specification at page 11, lines 22 to 23; page 27, line 26 to page 28, line 2; page 30, lines 1 to 12; page 32, line 27 to page 33, line 1. Accordingly, no prohibited new matter has been added by way of these amendments.

The Office Action mailed February 3, 2006, has been carefully reviewed and the following remarks are made in response thereto. In view of the amendments and the following remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Rejection under 35 U.S.C. § 102(e)

Claims 83, 84, and 87 have been rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,113,907 to Khwaja *et al.* (hereinafter "Khwaja *et al.*"). Specifically, the Examiner asserts that the measurements of biological activities in Khwaja *et al.* (col. 26, lines 19-34; col. 40, Table 8; and col. 6, lines 53-54) are directed to measurements of gene expression thereby reading on the claimed method of the present application.

Applicants have amended Claim 83 to specifically recite that the differential gene expression profile is determined by using a genomic-based bioassay method and to replace the term "molecular markers" with "genes". Support for this amendment can be found at least in the title and the specification at page 21, lines 9 to 10; page 28, lines 5 to 14; page 44, lines 7 to 12;

and page 44, lines 16 to 17. Thus, no prohibited new matter has been added by way of these amendments.

Applicants respectfully submit that the claimed method, as amended, is not anticipated by Khwaja *et al.* because the applied reference fails to disclose each and every limitation of the claimed method, as amended. More specifically, Khwaja *et al.* do not disclose a quality control method comprising determining differential gene expression profiles as compared with an untreated control of the characterized biosystem by using a genomic-based bioassay method and obtaining arrays of gene expression changes for two or more genes.

It is axiomatic that a claim is anticipated only if each and every element as set forth in the claim is described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

First, the determination of differential gene expression profiles in the claimed method is markedly different from the measurements of biological activities disclosed in Khwaja *et al.* Specifically, determination of differential gene expression profile involves measuring the gene expression levels of multiple genes which may or may not have any relationship to any diseases but still monitor batch to batch equivalency, while measurements of biological activities of Khwaja *et al.* involves the use of single enzyme or protein receptor with known relationship to a specific disease or therapeutic mechanism as the surrogate biomarker.

With respect to differential gene expression, it is well known in the art that different cell types make different proteins even though their genomes are identical. In other words, although most of the different cell types in the same organism contain the same set of genes, these different cells express somewhat different subsets of genes. That is, differential gene expression involves different gene expression levels for multiple genes. The claimed method in the present application involves, *inter alia*, determining the differential gene expression profiles of a biosystem with and without the biosystem being exposed to a whole batch of a herbal composition and then obtaining an array of gene expression alterations for two or more genes.

In contrast, the bioactivity assays in Khwaja *et al.* involves single enzyme or protein receptor known to be associated with a specific disease as the surrogate biomarker to assess the biological efficacy of a compound or substance in treating certain specific diseases. There is no disclosure or remote suggestion in Khwaja *et al.* as to the measurement of an overall biosystem's

response monitored by expression changes in the entire genome , i.e., alterations in differential gene expression profiles, when exposed to a whole batch of a herbal composition.

With respect to the disclosure of Khwaja *et al.* in col. 26, lines 17-34, it discusses measurement of antiviral activity of drugs. Khwaja *et al.* disclose that the reduction or elimination of cytopathic effects of HIV is estimated by studying the amount of the expression of viral reverse transcriptase. Khwaja *et al.* specifically states that a decreased expression of the viral enzyme would support antiviral effect of the drug treatment. That is, Khwaja *et al.* believe that the expression of viral protein reverse transcriptase directly correlates to the amount of the specific enzyme activity, which in turn reflects the amount of active HIV. In other words, Khwaja *et al.* disclose the use of a specific enzyme known to be associated to HIV infection as a surrogate biomarker to assess the biological activity of a drug against HIV.

Turning to the disclosure in Khwaja *et al.* in col. 6, lines 50-59 and col. 40, Table 8, Khwaja *et al.* state that St. John's Wort extract inhibits serotonin receptor expression (col. 6, lines 50-59) and further disclose the serotonin reuptake effects of different fractions of St. John's Wort extract (col. 40, Table 8). Based on Table 8, Khwaja *et al.* confirms the serotonin uptake activity of hypericin, a chemical compound in St. John's Wort extract (col. 40, lines 49-50). It is well known in the field of neurochemistry that serotonin receptors are receptors for the neurotransmitter and peripheral signal mediator serotonin (also known as 5-HT), which is known to be associated with several psychotic disorders including clinical depression, obsessive-compulsive disorder (OCD), migraine, bipolar disorder, anxiety disorders, and etc. That is, Khwaja *et al.* disclose the use a specific protein receptor, namely, serotonin receptor, which is known to be associated with certain psychotic disorders, as a surrogate biomarker to assess the bioactivity of different fractions of St. John's Wort extract in the treatment of the psychotic disorders.

Thus, the expression of enzyme or protein receptor disclosed in Khwaja *et al.* merely relate to the use of that single enzyme or protein receptor known to be associated with a specific disease as a surrogate biomarker to evaluate the therapeutic effect of a compound or substance in the treatment of the specific disease. This use of single enzyme or protein receptor is based on disease mechanism. In other words, the basis for this use of single enzyme or protein receptor is the knowledge that the single enzyme or protein receptor is known to be associated with a

biological pathway of a specific disease. In contrast, the determination of differential gene expression profiles in the present invention involves measuring gene expression levels of multiple genes including the whole genome, which may or may not have any relationship to any diseases thereby markedly differing from the expression of enzyme or protein receptor disclosed in Khwaja *et al.*

Second, the claimed method in steps (b) and (c) comprising, *inter alia*, obtaining an array of gene expression changes for two or more genes, while the Khwaja et al. do not disclose or remotely suggest measuring an array of gene expression alterations for two or more genes, as claimed in the present application. As discussed above, the expression of enzyme or protein receptor disclosed in Khwaja *et al.* involves only single enzyme or protein receptor and the use thereof for evaluating the bioactivity of a compound of substance in treating a specific disease. In contrast, the claimed method, *inter alia*, measures a biosystem's response, i.e., alterations in differential gene expression profiles for two or more genes, when exposed to a whole batch of a herbal composition.

Third, the claimed method, as amended, uses genomic-based bioassay methods to determine the differential gene expression profiles, while Khwaja *et al.* do not disclose or remotely suggest the use of genomic-based method in the bioassay disclosed therein. In fact, Khwaja *et al.* specifically states that "enzymatic and receptor based assays are preferable in the practice of this invention." (Khwaja *et al.*, Section 5.4.1, col. 23, lines 10-12)

Fourth, the claimed method is based on measuring the biological response of a biosystem when the biosystem is exposed to a whole batch, not fractions, of a herbal composition, while PharmaPrint® method of Khwaja *et al.* is based on measuring series of biological activities of the individual fractions of St. John's Wort extract. Specifically, the methods disclosed in Khwaja *et al.* comprise the step of separating the botanical composition into a plurality of marker fractions and determining the biological activity of each of the marker fractions to provide a bioactivity fingerprint (col. 9, lines 9-14; col. 9, lines 24-30; col. 9, lines 56-62; and Fig. 6). In contrast, steps (b)(i) and (c)(i) indicate that the biosystem is exposed to a whole batch of a herbal composition, either the standard batch or the test batch, not a fraction or fractions of any batch.

Fifth, although it is true that both Khwaja *et al.* and the present invention have the similar objectives of resolving the quality control problem in botanical or herbal compositions, Khwaja

et al. and the present invention are directed to fundamentally different ways to achieve their goals. It is common knowledge that the basic concept of quality control typically involves selecting a standard, collecting data on the standard and a test sample, and comparing the data of the test sample and the standard. However, it is important to note that the same end can be achieved through different means. In other words, different quality control methods can carry out the basic concept of quality control in markedly different ways. As discussed above, Khwaja *et al.* uses fractionation and standard enzyme/protein receptor assays that are implicated in the disease to carry out the quality control method disclosed therein; while the present invention uses the whole herbal extract and the pattern of gene changes of the biosystem's genome to carry out the claimed method. Applicants respectfully submit that using gene changes to carry out a quality control method is markedly different from using enzyme or protein receptor changes to screen bioactivity of chemical substance or investigate mechanism of a disease. Furthermore, Applicants respectfully draw the Examiner's attention to the Declaration under 37 C.F.R. § 1.132 by Dr. Dan Theodorescu dated March 7, 2005 (hereinafter "the Declaration"). In paragraph 2 of the Declaration, Dr. Theodorescu states that the present application discloses and claims a quality control method including comparing the genomic expression pattern (*i.e.*, test bioresponse array) generated by exposing a biosystem to the herbal composition to a genomic expression pattern (*i.e.*, standardized herbal bioresponse array) collected from the same or substantially the same herbal composition that is considered the herbal standard. In paragraph 5 of the Declaration, Dr. Theodorescu states that Khwaja et al. disclose using compositional and bioactivity fingerprints for the processing of St. John's Wort to produce botanical drugs and the methods taught by Khwaja *et al.* do not include using gene expression profiles for quality control.

In view of the foregoing, not only the methods of Khwaja *et al.* are fundamentally different from the claimed method, but also Khwaja *et al.* fail to disclose or suggest at least the following aspects of the claimed method, as amended: (1) determining differential gene expression profiles, (2) obtaining an array of gene expression alterations for two or more genes, (3) using genomic-based bioassay methods, and (4) exposing the biosystem to a whole batch of a herbal composition. Since the applied reference fails to disclose some essential elements of the claimed method, as amended, the applied reference does not anticipate the present invention.

In view of the claim amendments and the foregoing remarks, Applicants respectfully request that the rejections under 35 U.S.C. § 102(e) be withdrawn.

Conclusion

In view of the foregoing remarks, Applicants respectfully request withdrawal of the outstanding rejection and early notice of allowance to that effect. Should the Examiner believe that a telephonic interview would expedite prosecution and allowance of this application, he is encouraged to contact the undersigned at his convenience.

Except for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No.50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Dated: March 5, 2007

Respectfully submitted,
COOLEY GODWARD KRONISH LLP

By: _____
Yong Lu
Reg. No. 56,038

Cooley Godward Kronish LLP
ATTN: Patent Group
The Bowen Building
875 15th Street NW, Suite 800
Washington, DC 20005-2221
Tel: (202) 842-7861 or
(703) 456-8000
Fax: (202) 842-7899